FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
220316US0PCT	10/088090

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB00/01382	28 September 2000	28 September 1999

TITLE OF INVENTION
PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES

APPLICANT(S) FOR DO/EO/US
Stephen ARKINSTALL et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice of Priority/ Form PTO-1449
References Cited (5)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/088090	PCT/IB00/01382	220316US0PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	28 - 20 =	8	x $18.00	$144.00	
Independent claims	3 - 3 =	0	x $84.00	$0.00	
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,164.00	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$1,164.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00	
TOTAL NATIONAL FEE =				$1,164.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00	
TOTAL FEES ENCLOSED =				$1,164.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$1,164.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Surinder Sachar
Registration No. 34,423

22850

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

March 21 2002
DATE

Docket No. 220316US0PCT
IN RE APPLICATION OF: Stephen ARKINSTALL, et al.
SERIAL NO: New U.S. PCT Application
FILED: HEREWITH
FOR: PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required

☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 is claimed.

☒ Additional documents filed herewith: PCT Transmittal Letter/Check for $1,164.00/Notice of Priority
Information Disclosure Statement/Form PTO-1449/References Cited (5)
International Search Report/International Preliminary Examination Report

The Fee has been calculated as shown below:

CLAIMS	CLAIMS REMAINING		HIGHEST NUMBER PREVIOUSLY PAID	NO. EXTRA CLAIMS	RATE	CALCULATIONS
TOTAL	28	MINUS	28	0	× $18 =	$0.00
INDEPENDENT	3	MINUS	3	0	× $84 =	$0.00
		☐ MULTIPLE DEPENDENT CLAIMS			+ $280 =	$0.00
		TOTAL OF ABOVE CALCULATIONS				$0.00
		☐ Reduction by 50% for filing by Small Entity				$0.00
		☐ Recordation of Assignment			+ $40 =	$0.00
					TOTAL	$0.00

☐ A check in the amount of **$0.00** is attached.

☒ Please charge any additional Fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

☒ If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. §1.136, and any additional fees required under 37 C.F.R. §1.136 for any necessary extension of time may be charged to Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No. 24,618

Surinder Sachar
Registration No. 34,423

22850
Customer Number 22850
Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 10/01)

220316US-0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

STEPHEN ARKINSTALL ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW U.S. PCT APPLN :
(Based on PCT/IB00/01382)

FILED: HEREWITH :

FOR: PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown on the marked-up copy following this amendment to read as follows.

3. (Amended) A sulfonyl amino acid derivatives according to claim 1, wherein n is 1.

4. (Amended) A sulfonyl amino acid derivative according to claim 1, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, said residues being optionally substituted by at least one substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy,

substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, substituted or unsubstituted C_1-C_6- thioalkoxy.

5. (Amended) A sulfonyl amino acid derivative according to claim 1, wherein at least one of R^3 and/or R^4 is selected from the group consisting of the following natural amino acid residues : alanyl, arginyl, asparaginyl, aspartyl, cysteinyl, glutaminyl, glutamyl, glycyl, histidyl, isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl, tryptophanyl, tyrosyl, valyl.

6. (Amended) A sulfonyl amino acid derivative according to claim 1, wherein

Ar^1 is an unsubstituted or substituted phenyl, preferably 4-chlorophenyl, X is O, R^1, R^2, R^3 and R^4 are hydrogen, n is 1, Ar^2 is thienyl, R^5 is H or C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl - e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstituted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl;

said aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6- thio alkoxy; or

R^5 and R^6 taken together could form an unsubstituted or substituted 4-8-membered saturated cyclic alkyl or heteroalkyl group, e.g. an unsubstituted or substituted piperidino group.

7. (Amended) A sulfonyl amino acid derivative according to claim 1, wherein

R^5 is H; and R^6 is a C_1-C_6-alkyl which is substituted by an aryl, an heteroaryl group or an aminoaryl, aminoheteroaryl, aryloxy, heteroaryloxy, whereby said aryl and heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, substituted or unsubstituted aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6-thioalkoxy.

9. (Amended) A sulfonyl amino acid derivative according to claim 1 which is selected from the following group :

4-chloro-N-({5-[({2-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]-2-oxoethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[(2-{[2-({5-nitropyridin-2-yl}amino)ethyl]amino}-2-oxoethyl)-amino]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

N-({5-[({2-[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]-2-oxoethyl}amino)-sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

4-chloro-N-[(5-{[(2-oxo-2-{3-[(trifluoromethyl)sulfonyl]anilino}ethyl)amino]-sulfonyl}thien-2-yl)methyl]benzamide.

12. (Amended) Use according to claim 10 for the treatment or prevention of disorders associated with abnormal expression or activity of JNK2 and/or 3.

13. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular claim 10 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases, spinal cord injury, head trauma.

14. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular according to claim 10 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

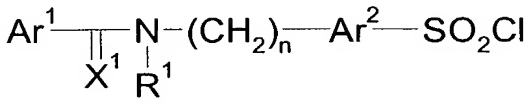
15. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular according to claim 10 for the treatment of cancer including breast-, colorectal-, pancreatic cancer.

16. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular according to claim 10 for the treatment of cardiovascular diseases including stroke, arteriosclerosis, myocordial infarction, myocordial reperfusion injury.

17. (Amended) A pharmaceutical composition containing at least one sulfonyl amino acid derivative according to claim 1 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

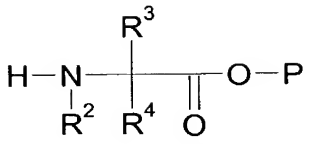
18. (Amended) Process for the preparation of a sulfonyl amino acid derivative according to claim 1 comprising or consisting of the steps of:

a) preparing a sulfonyl compound V,



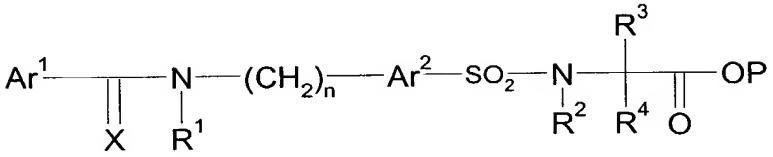
V

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



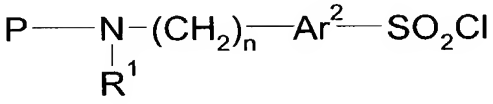
IX

c) said compound IX is subjected to a deprotection and finally

d) a coupling.

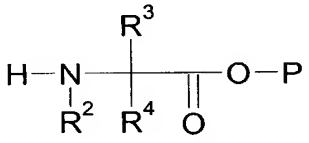
19. (Amended) Process for the preparation of the sulfonyl amino acid derivatives according to claim 1 comprising or consisting of the steps of:

a) preparing a protected sulfonyl compound VII



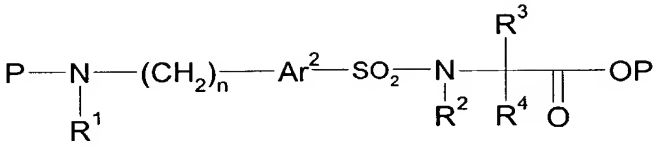
VII

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



X

e) followed by deprotection;

f) coupling;

g) deprotection, and

h) acylation.

Please add the following new claims.

20. (New) A sulfonyl amino acid derivative according to claim 2, wherein n is 1.

21. (New) A sulfonyl amino acid derivative according to claim 2, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, said residues being optionally substituted by at least one substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, substituted or unsubstituted C_1-C_6- thioalkoxy.

22. (New) A sulfonyl amino acid derivative according to claim 2, wherein at least one of R^3 and/or R^4 is selected from the group consisting of the following natural amino acid residues : alanyl, arginyl, asparaginyl, aspartyl, cysteinyl, glu-taminyl, glutamyl, glycyl, histidyl, isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl, tryptophanyl, tyrosyl, valyl.

23. (New) A sulfonyl amino acid derivative according to claim 2, wherein

Ar^1 is an unsubstituted or substituted phenyl, preferably 4-chlorophenyl, X is O, R^1, R^2, R^3 and R^4 are hydrogen, n is 1, Ar^2 is thienyl, R^5 is H or C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl - e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino

heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstituted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl;

said aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6- thio alkoxy; or

R^5 and R^6 taken together could form an unsubstituted or substituted 4-8-membered saturated cyclic alkyl or heteroalkyl group, e.g. an unsubstituted or substituted piperidino group.

24. (New) A sulfonyl amino acid derivative according to claim 2, wherein

R^5 is H; and R^6 is a C_1-C_6-alkyl which is substituted by an aryl, an heteroaryl group or an aminoaryl, aminoheteroaryl, aryloxy, heteroaryloxy, whereby said aryl and heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, substituted or unsubstituted aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6-thioalkoxy.

25. (New) A sulfonyl amino acid derivative according to claim 24 which is selected from the following group :

4-chloro-N-({5-[({2-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]-2-oxoethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[(2-{[2-({5-nitropyridin-2-yl}amino)ethyl]amino}-2-oxoethyl)-amino]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

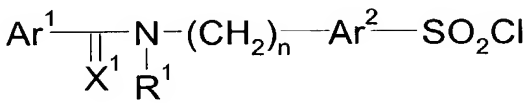
N-({5-[({2-[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]-2-oxoethyl}amino)-sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

4-chloro-N-[(5-{[(2-oxo-2-{3-[(trifluoromethyl)sulfonyl]anilino}ethyl)amino]-sulfonyl}thien-2-yl)methyl]benzamide.

26. (New) A pharmaceutical composition containing at least one sulfonyl amino acid derivative according to claim 2 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

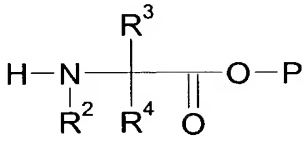
27. (New) Process for the preparation of a sulfonyl amino acid derivative according to claim 2 comprising or consisting of the steps of:

a) preparing a sulfonyl compound V,



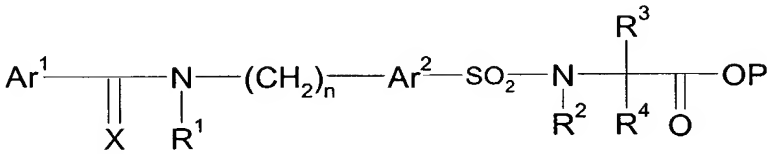
V

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



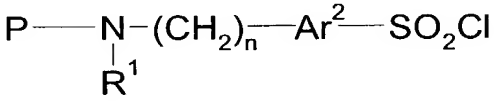
IX

c) said compound IX is subjected to a deprotection and finally

d) a coupling.

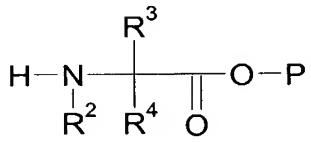
28. (New) Process for the preparation of the sulfonyl amino acid derivatives according to claim 2 comprising or consisting of the steps of:

a) preparing a protected sulfonyl compound VII



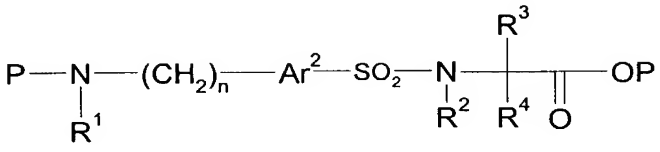
VII

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



X

e) followed by deprotection;

f) coupling;

g) deprotection, and

h) acylation.

REMARKS

Claims 1-28 are active in the present application. Claims 20-28 are new claims. Support for the new claims is found in the original claims. Claims 3-7, 9 and 11-19 have been amended to remove multiple dependencies. No new matter is added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Stefan U. Koschmieder, Ph.D.
Registration No. 50,238

22850
Tel.: (703) 413-3000
Fax: (703) 413-2220
NFO:SUK\la
220316US-236532-236533-0-PCT

220316US-0PCT

Marked-Up Copy

Serial No: _____

Amendment Filed on: 3-21-2002

IN THE CLAIMS

Please amend the claims as follows.

--3. (Amended) A sulfonyl amino acid derivatives according to claim 1 [or 2], wherein n is 1.

4. (Amended) A sulfonyl amino acid derivative according to [any of the preceding claims] claim 1, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, said residues being optionally substituted by at least one substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, substituted or unsubstituted C_1-C_6- thioalkoxy.

5. (Amended) A sulfonyl amino acid derivative according to [any of the preceding claims] claim 1, wherein at least one of R^3 and/or R^4 is selected from the group consisting of the following natural amino acid residues : alanyl, arginyl, asparaginyl, aspartyl, cysteinyl, glu-taminyl, glutamyl, glycyl, histidyl, isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl, tryptophanyl, tyrosyl, valyl.

6. (Amended) A sulfonyl amino acid derivative according to [any of the preceding claims] claim 1, wherein

Ar^1 is an unsubstituted or substituted phenyl, preferably 4-chlorophenyl, X is O, R^1, R^2, R^3 and R^4 are hydrogen, n is 1, Ar^2 is thienyl, R^5 is H or C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl - e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstituted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl;

said aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6- thio alkoxy; or

R^5 and R^6 taken together could form an unsubstituted or substituted 4-8-membered saturated cyclic alkyl or heteroalkyl group, e.g. an unsubstituted or substituted piperidino group.

7. (Amended) A sulfonyl amino acid derivative according to [any of the preceding claims] claim 1, wherein

R^5 is H; and R^6 is a C_1-C_6-alkyl which is substituted by an aryl, an heteroaryl group or an aminoaryl, aminoheteroaryl, aryloxy, heteroaryloxy, whereby said aryl and heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, substituted or unsubstituted aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6-thioalkoxy.

9. (Amended) A sulfonyl amino acid derivative according to [any of the preceding claims] claim 1 which is selected from the following group :

4-chloro-N-({5-[({2-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]-2-oxoethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[(2-{[2-({5-nitropyridin-2-yl}amino)ethyl]amino}-2-oxoethyl)-amino]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

N-({5-[({2-[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]-2-oxoethyl}amino)-sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

4-chloro-N-[(5-{[(2-oxo-2-{3-[(trifluoromethyl)sulfonyl]anilino}ethyl)amino]-sulfonyl}thien-2-yl)methyl]benzamide.

12. (Amended) Use according to claim 10 [or 11] for the treatment or prevention of disorders associated with abnormal expression or activity of JNK2 and/or 3.

13. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular [according to any of claims 10 to 12] claim 10 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases, spinal cord injury, head trauma.

14. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular according to [any of claims 10 to 12] claim 10 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

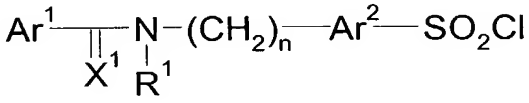
15. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular according to [any of claims 10 to 12] claim 10 for the treatment of cancer including breast-, colorectal-, pancreatic cancer.

16. (Amended) Use of a sulfonyl amino acid derivative according to formula I in particular according to [any of claims 10 to 12] claim 10 for the treatment of cardiovascular diseases including stroke, arteriosclerosis, myocordial infarction, myocordial reperfusion injury.

17. (Amended) A pharmaceutical composition containing at least one sulfonyl amino acid derivative according to [any of the claims 1 to 9] claim 1 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

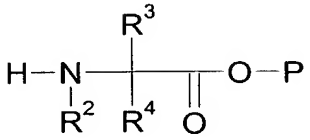
18. (Amended) Process for the preparation of a sulfonyl amino acid derivative according to [any of the claims 1 to 9] claim 1 comprising or consisting of the steps of:

e) preparing a sulfonyl compound V,



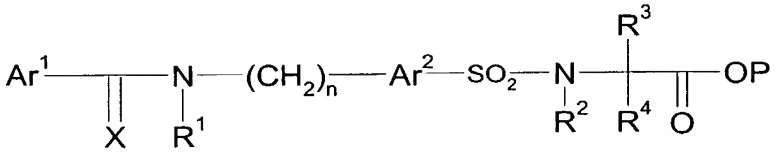
V

f) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



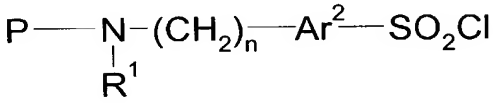
IX

g) said compound IX is subjected to a deprotection and finally

h) a coupling.

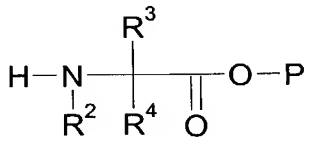
19. (Amended) Process for the preparation of the sulfonyl amino acid derivatives according to [any of the claims 1 to 9] claim 1 comprising or consisting of the steps of:

a) preparing a protected sulfonyl compound VII



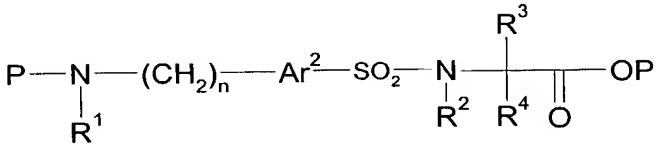
VII

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



X

e) followed by deprotection;

f) coupling;

g) deprotection, and

h) acylation.--

Claims 20-28 (New).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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99810871.6 28 September 1999 (28.09.1999) EP

(71) Applicant *(for all designated States except US)*: **APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.** [NL/NL]; Pietermaai 15, Curacao (AN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARKINSTALL, Stephen** [GB/FR]; La Bergerie/les Goths, F-74350 Cruseilles (FR). **HALAZY, Serge** [FR/FR]; 3, allée des Jonquilles, F-74100 Vetraz-Monthoux (FR). **CHURCH, Dennis** [US/CH]; 4, chemin des Vignes, CH-1291 Commugny (CH). **CAMPS, Montserrat** [ES/CH]; 7, chemin du Pré-Colomb, CH-1290 Versoix (CH). **RUECKLE, Thomas** [DE/CH]; 142A, route de St. Julien, CH-1228 Plan-les-Ouates (CH). **GOTTELAND, Jean-Pierre** [FR/FR]; 423, chemin des Crets, F-74160 Beaumont (FR). **BIAMONTE, Marco** [US/CH]; 13, rue St. Joseph, CH-1227 Carouge (CH).

(74) Agents: **MOINAS, Michel** et al.; Moinas Savoye & Cronin, 42, rue Plantamour, CH-1201 Geneva (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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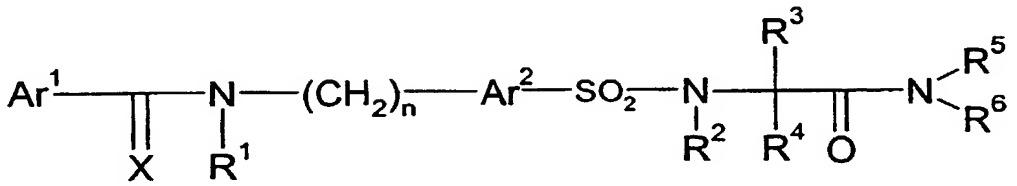
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES



(I)

(57) Abstract: The present invention is related to sulfonyl amino acid derivatives of formula (I), notably for use as pharmaceutically active compounds, as well as to pharmaceutical formulations containing such sulfonyl amino acid derivatives. Said sulfonyl amino acid are efficient modulators of the JNK pathway, they are in particular efficient inhibitors of JNK 2 and 33. The present invention is furthermore related to novel sulfonyl amino acid derivatives as well as to methods of their preparation.

WO 01/23379 A1

US 460

10088090 .27 JUN 2002

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ORIGINAL

10/088090

Declaration, Power of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES

the specification of which

☐ is attached hereto.

☒ was filed on 21 March 2002 as

Application Serial No. 10/088,090

and amended on _____.

☒ was filed as PCT international application

Number PCT/IB00/01382

on 28 September 2000,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

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99810871.6	Europe	28 September 1999	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

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Stephen ARKINSTALL
NAME OF FIRST SOLE INVENTOR

Signature of Inventor

13 May 2002
Date

Residence: 31 Marsh Street
Belmont 02478 MA - USA USA

Citizen of: Great Britain

Mailing Address: Same as above

10/01

Serge HALAZY
NAME OF SECOND JOINT INVENTOR

Residence: Allée des Jonquilles 3
F-74100 Vetraz-Monthoux, France

✓
Signature of Inventor

Citizen of: France
Mailing Address: Same as above

✓
Date

Dennis CHURCH
NAME OF THIRD JOINT INVENTOR

Residence: Chemin des Vignes 4
CH-1291 Commugny, Switzerland

✓
Signature of Inventor

Citizen of: United States
Mailing Address: Same as above

✓
Date

Montserrat CAMPS
NAME OF FOURTH JOINT INVENTOR

Residence: Chemin du Pré-Colomb 7
CH-1290 Versoix, Switzerland

✓
Signature of Inventor

Citizen of: Spain
Mailing Address: Same as above

✓
Date

Thomas RUECKLE
NAME OF FIFTH JOINT INVENTOR

Residence: Route de St. Julien 142A
CH-1228 Plan-les-Ouates, Switzerland

✓
Signature of Inventor

Citizen of: Germany
Mailing Address: Same as above

✓
Date

Jean Pierre GOTTELAND
NAME OF SIXTH JOINT INVENTOR

Residence: Chemin des Crets 423
F-74160 Beaumont, France

✓
Signature of Inventor

Citizen of: France

Mailing Address: Same as above

✓
Date

Marco BIAMONTE
NAME OF SEVENTH JOINT INVENTOR

Residence: Flore Terrace, Apt 203
San Diego, CA 92122 - USA

✓
Signature of Inventor

Citizen of: United States

Mailing Address: Same as above

✓
Date

NAME OF EIGHTH JOINT INVENTOR

Residence:

Signature of Inventor

Citizen of:

Mailing Address:

Date

NAME OF NINTH JOINT INVENTOR

Residence:

Signature of Inventor

Citizen of:

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10/088090 - 052402

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CA

✓
Signature of Inventor

Citizen of: United States
Mailing Address: Same as above

✓ May 24th 2002
Date

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Residence:

Signature of Inventor

Citizen of:
Mailing Address:

Date

NAME OF NINTH JOINT INVENTOR

Residence:

Signature of Inventor

Citizen of:
Mailing Address:

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Residence: La Bergerie/Les Goths
F-74350 Cruseilles, France

/
Signature of Inventor

Citizen of: Great Britain

Mailing Address: Same as above

/
Date

2W

Serge ~~HALAZY~~
NAME OF SECOND JOINT INVENTOR

✓
Signature of Inventor

✓ May 2, 2002
Date

Residence: Allée des Jonquilles 3
F-74100 Vetraz-Monthoux, France FRX

Citizen of: France
Mailing Address: Same as above

3W

Dennis CHURCH
~~NAME OF THIRD~~ JOINT INVENTOR

✓
Signature of Inventor

✓ 1/MAY/02
Date

Residence: Chemin des Vignes 4
CH-1291 Commugny, Switzerland CHX

Citizen of: United States
Mailing Address: Same as above

4W

Montserrat CAMPS
~~NAME OF FOURTH JOINT~~ INVENTOR

✓
Signature of Inventor

✓ 30/04/02
Date

Residence: Chemin du Pré-Colomb 7
CH-1290 Versoix, Switzerland CHX

Citizen of: Spain
Mailing Address: Same as above

5W

Thomas RUECKLE
NAME OF FIFTH JOINT INVENTOR

✓ 30/4/02
Signature of Inventor

✓
Date

Residence: Route de St. Julien 142A
CH-1228 Plan-les-Ouates, Switzerland CHX

Citizen of: Germany
Mailing Address: Same as above

Jean Pierre GOTTELAND
NAME OF SIXTH ~~JOINT~~ INVENTOR

Residence: Chemin des Crets 423
F-74160 Beaumont, France FRX

Signature of Inventor

Citizen of: France

Mailing Address: Same as above

30/04/02
Date

Marco BIAMONTE
NAME OF SEVENTH JOINT INVENTOR

Residence: Rue St. Joseph 13
CH-1227 Carouge, Switzerland

Signature of Inventor

Citizen of: United States

Mailing Address: Same as above

Date

NAME OF EIGHTH JOINT INVENTOR

Residence:

Signature of Inventor

Citizen of:

Mailing Address:

Date

NAME OF NINTH JOINT INVENTOR

Residence:

Signature of Inventor

Citizen of:

Mailing Address:

Date